1.3.1 Summary of product characteristics (SmPC)

Summary of products characteristics (SmPC) of Myclav Powder for Oral Suspension 156.25 mg/ 5 ml (Amoxicillin and Clavulanate Potassium for Oral Suspension USP) is enclosed overleaf.

6. Summary of Product Information

1. Name of the Medicinal Product

1.1 Product name : MYCLAV POWDER FOR ORAL SUSPENSION 156.25MG/5ML

1.2 Strength : 156.25 MG / 5 ML

1.3 Pharmaceutical Dosage form : Oral Suspension

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration : The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.
Refer Standard unit formula enclosed overleaf.

2.2 Quantitative Declaration : The quantity of the active substance must be expressed per dosage unit (for metered dose inhalation products, per puff) per unit volume or per unit of weight).
Refer Standard unit formula enclosed overleaf.

Sr. No.	Ingredients	Qty/Bottle in g	Function
1.	Amoxicillin Trihydrate USP (Purimox extra dry)	2.500	Active
2.	Potassium Clavulanate Diluted Ph.Eur (1:1 blend with Silicon Dioxide)	1.638	Active
3.	Silicon Dioxide USP/NF	5.016	Diluent
4.	Xanthan Gum USP/NF	0.174	Suspending agent
5.	Hypromellose (5 cps) Ph.Eur/BP	1.115	Viscosity building agent
6.	Silica, Colloidal Anhydrous Ph.Eur/BP	0.350	Glidant
7.	Succinic Acid USP/NF	0.012	Preservative
8.	Aspartame BP	0.175	Sweetener
9.	Orange Flavour Dry 0471034	0.510	Flavour
10.	Raspberry Flavour Dry 0473005	0.510	Flavour
	Total	**12.00**	

3. Pharmaceutical Form

White to off- white free flowing powder, which on reconstitution gives white to off- white coloured liquid suspension.

Powder for oral suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indication(s)

1. Lower Respiratory Tract Infections - caused by beta-lactamase-producing isolates of Haemophilus influenzae and Moraxella catarrhalis.
2. Acute Bacterial Otitis Media - caused by beta-lactamase-producing isolates of H. influenzae and M. catarrhalis.
3. Sinusitis- caused by beta-lactamase- producing isolates of H. influenzae and M. catarrhalis.
4. Skin and Skin Structure Infections - caused by beta-lactamase-producing isolates of Staphylococcus aureus, Escherichia coli, and Klebsiella species.
5. Urinary Tract Infections-caused by beta-lactamase-producing isolates of E. coli, Klebsiella species, and Enterobacter species.

4.2 Posology and method of administration

Doses are expressed throughout in terms of amoxicillinlclavulanic acid content except when doses are stated in terms of an individual component.

Neonates and Infants Aged <12 weeks (<3 months):
The recommended dose of amoxicillin and clavulanate potassium is 30 mq/kg/day divided every 12 hours, based on the amoxicillin component. Experience with the 228.5 mg/5 ml formulation in this age group is limited, and thus, use of the 156.25 mg/5 ml oral suspension is recommended.

Patients Aged 12 weeks (3 months) and Older:
The every 12 hour regimen is recommended as it is associated with significantly less diarrhea.(See dosing regimens provided in below Table).

Dosing in Patients Aged 12 weeks (3 months) and Older

INFECTION	DOSING REGIMEN	
	Every 12 hours	Every 8 hours
	228.5 mg/5 ml oral suspension	156.25 mg/5 ml oral suspension
Otitis media, sinusitis, lower respiratory tract infections and more severe infections	45 mg/kg/day*every 12 hours	40 mg/kg/day*every 8 hours
Less severe infections	25 mg/kg/day*every 12 hours	20 mg/kg/day*every 8 hours

* Dosage are expressed in terms of amoxicillin component.
Duration of therapy studied and recommended for acute otitis media is 10 days.
For children ≥ 40 kg, adult dose should be given.

Direction for use :
Tap bottle gently until all the powder flows freely. Add water to approximately 213 of the fill line on the bottle (shown by a circularring mark for 156.25 mgl5 ml & shown by a line for 228.5 mg/5 ml). Replace the cap, and shake the bottle until all the powder is suspended. Add more

water until the level of the fill line is attained, and shake again. When first reconstituted, allow to stand for 5 minutes to ensure full dispersion.

Use In Specific Populations:

Pregnancy:
Teratogenic Effects: Pregnancy Category B. Reported evidence suggests that if pregnant rats and mice were given amoxicillin and clavulanic acid (2:1 ratio formulation of amoxicillin: clavulanate) at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to amoxicillin and clavulanlc acid. The amoxicillin doses in rats and mice (based on body surface area) were approximately 4 and 2 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, these dose multiples were approximately 9 and 4 times the maximum recommended adult human oral dose (125 mg every 8 hours). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:
Oral ampicillin-class antibiotics reported to be absorbed poorly during labor. lt is not known whether use of amoxicillin/clavulanate potassium in humans during tabor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood of the necessity for an obstetrical intervention.

Nursing Mothers:

Amoxicillin has been reported to be excreted in human milk. Amoxicillin/clavulanate potassium use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin/clavulanate potassium is administered to a nursing woman.

Paediatric Use:

Evidence suggests that amoxicillin and clavulanic acid combination powder for oral suspension has been safe and effective in paediatric patients. Reported evidence from studies of amoxicillin and clavulanic acid combination tablets in adults with additional data from a study of amoxicillin and clavulanic acid combination powder for oral suspension in paediatric patients aged 2 months to 12 years with acute otitis media supports the use amoxicillin and clavulanic acid combination for paediatric use. Evidence suggests that because of incompletely developed renal function in neonates and young infants, the elimination of amoxicillin may be delayed; clavulanate elimination is unaltered in this age group. Dosing of amoxicillin and clavulanic acid combination should be modified in paediatric patients aged <12 weeks (<3 months).
Geriatric Use: Reported evidence suggests that, there Is no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported evidence has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. lt has been reported that this drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this

drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Dosing in Renal Impairment:
Amoxicillin is primarily eliminated by the kidney and dosage adjustment is usually required in patients with severe renal impairment (GFR <30 mL/min).

Method of administration : Oral

4.3 Contra-indications

1. Serious Hypersensitivity Reactions: Amoxicillin and clavulanate potassium is contraindicated in patients witha history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to amoxicillin, clavulanate or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins).
2. Cholestatic Jaundice/Hepatic Dysfunction: Amoxicillin and clavulanate potassium is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with amoxicillin and clavulanate potassium.Beta-blockers should be used with caution in patients with peripheral vascular disease.

4.4 Special warnings and precautions for use

Hypersensitivity Reactions:
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving bela-lactam antibacterials. These reactions are more likely to occur in individuals with a history of penicillin hypersens~ivity and/or a history of sensitivity to multiple allergens. Before initiating therapy with amoxicillin and clavulanate potassium combination, careful inquiry should be made regarding previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be iscontinued and appropriate therapy instituted.

Hepatic Dysfunction:
Reported evidence suggests that hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of amoxicillin and clavulanate potassium combination,. Hepatic toxicity is usually reversible; however, deaths have been reported. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

Clostridium difficile Associated Diarrhea (GOAD):
Reported evidence suggests that Clostridium difficile associated diarrhea (CDAD) is associated with use of nearly all antibacterial agents, including of amoxicillin and clavulanate potassium combination, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile reported to cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be

considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated. Skin Rash in Patients with Mononucleosis: A high percentage of patients with mononucleosis who receive amoxicillin were reported to cause an erythematous skin rash. Thus, amoxicillin and clavulanate potassium combination should not be administered to patients with mononucleosis.

Potential for Microbial Overgrowth:
Reported evidence suggests thal there is a possibility of superinfections with fungal or bacterial pathogens should be considered during therapy. If superinfection occurs, amoxicillin/clavulanate potassium should be discontinued and appropriate therapy should be instituted
Phenylketonurics: This formulation should be used cautiously in patients with phenyketonuria.
Development of Drug-Resistant Bacteria: Reported evidence suggests that prescribing amoxicillin and clavulanate potassium in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient, and increases the risk of the development of drug-resistant bacteria.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid:
Probenecid decreases the renal tubular secretion of amoxicillin but does not delay renal excretion of clavulanic acid. Concurrent use with amoxicillin and clavulanic acid may result in increased and prolonged blood concentrations of amoxicillin. Go-administration of probenecid is not recommended.

Oral Anticoagulants:
Abnormal prolongation of prothrombin time (increased international normalized ratio [INR)) has been reported in patients receiving amoxicillin and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently with amoxicillin and clavulanic acid. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Allopurinol:
The concurrent administration of allopurinol and amoxicillin has been reported to cause rashes in patients receiving both drugs as compared to patients receiving amoxicillin alone. 1t is not known whether this potentiation or amoxicillin rashes is due to allopurinol or the hyperuricemia present in these patients.

Oral Contraceptives:
Amoxicillin and clavulanic acid combination has been reported to affect intestinal flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

Effects on Laboratory Tests:
Evidence suggests that high urine concentrations of amoxicillin may result in falsepositive reactions when testing for the presence of glucose in urine using, Benedict's Solution, or Fehling's Solution. Since this effect may also occur with amoxicillin and clavulanate potassium it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

Reported evidence suggests that following administration of amoxicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol has been noted.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Teratogenic Effects: Pregnancy Category B. Reported evidence suggests that if pregnant rats and mice were given amoxicillin and clavulanic acid (2:1 ratio formulation of amoxicillin: clavulanate) at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to amoxicillin and clavulanlc acid. The amoxicillin doses in rats and mice (based on body surface area) were approximately 4 and 2 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, these dose multiples were approximately 9 and 4 times the maximum recommended adult human oral dose (125 mg every 8 hours). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery:
Oral ampicillin-class antibiotics reported to be absorbed poorly during labor. lt is not known whether use of amoxicillin/clavulanate potassium in humans during tabor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood of the necessity for an obstetrical intervention.

Nursing Mothers:
Amoxicillin has been reported to be excreted in human milk. Amoxicillin/clavulanate potassium use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin/clavulanate potassium is administered to a nursing woman.

4.7 Effects on the ability to drive and use machines

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4.8 Undesirable effects

Gastrointestinal:
Indigestion, gastritis, stomatitis, glossitis, black "hairy tongue, mucocutaneous candidiasis,enterocolitis, and hemorrhagic/pseudomembranous colitis. Evidence suggests that symptoms of pseudomembranous colitis may be reported during or after antibiotic treatment.

Hypersensitivity Reactions:

Pruritus, angioedema, serum sickness- like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, hypersensitivity vasculitis, and cases of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported.
Liver Hepatic dysfunction, including hepatitis and cholestatlc jaundice, increases in serum transaminases (AST and/or ALT), serum bilirubin, and/or alkaline phosphatase, has been reported with amoxicillin and clavulanate potassium. Evidence suggests that it has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histological findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes.
lt is reported that the onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. Deaths have been reported.

Renal:
Interstitial nephritis, hematuria, and crystalluria have been reported.

Hematopoietic and Lymphatic Systems:
Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.
Thrombocytosis was noted in less than 1% of the patients treated with amoxicillin and clavulanate potassium combination. Evidence suggests that in patients receiving amoxicillin and clavulanate potassium combination and anticoagulant therapy concomitantly, increased prothrombin time was observed.

Central Nervous System:
Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported.

Miscellaneous:
Tooth discoloration (brown, yellow, or gray staining) has been reported. Most reports occurred in pediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

4.9 Overdose
In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action:
Amoxicillin is a semisynthetic antibiotic with in vitro bactericidal activity against Grampositive and Gram-negative bacteria. Amoxicillin is, however, susceptible to degradation by beta-

lactamases, and therefore, the spectrum of activity does not include organisms which produce these enzymes. Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate some beta-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance. The formulation of amoxicillin and clavulanic acid protects amoxicillin from degradation by some beta-lactamase enzymes and extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin.

Pharmacodynamics:
Amoxicillin/clavulanic acid has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections. Gram positive bacteria: Staphylococcus aureus Gram negative bacteria: E. Coli, Enterobacter species, Haemophilus influenzae, Klebsiella species, Moraxella catarrhalis, The following in vitro data is reported, but their clinical significance is unknown.

At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for amoxicillin/clavulanic acid. However, the efficacy of amoxicillin/clavulanic acid in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials Gram positive bacteria: Enterococcus faecalis, Staphylococcus saprophyticus, staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes, Viridans streptococci, Gram negative bacteria: Eikenella corrodens, Proteus mirabilis Anaerobic bacteria: Bacteroides species including Bacteroides fragilis, Fusobacterium species, peptostreptococcus.

5.2 Pharmacokinetic properties

Absorption:
Reported evidence suggests that dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin and clavulanic acid combination can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state. Reported evidence suggests that, the relative bioavailability of clavulanate was reduced when amoxicillin and clavulanic acid combination was dosed at 30 and 150 minutes after the start of a high-fat breakfast.

Distribution:
Neither component in amoxicillin and clavulanic acid combination is reported to be highly proteinbound. Evidence suggests that clavulanic acid is approximately 25% bound to human serum and amoxicillin approximately 18% bound.
Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. Two hours after oral administration of a single 35 mg/kg dose of suspension of amoxicillin and clavulanic acid combination to fasting children, average concentrations of 3 mcg/ml of amoxicillin and 0.5 mcg/ml of clavulanic acid were reported in middle ear effusions.

Metabolism and Excretion:
The reported half-life of amoxicillin after the oral administration of amoxicillin and clavulanic acid combination is 1.3 hours and that of clavulanic acid is 1 hour. Evidence suggests that approximately 50% to 70% of the amoxicillin and approximately 25% to 40% of the clavulanic acid are excreted unchanged in urine during the first 6 hours after administration of a single 250-mg or 500-mg tablet of amoxicillin and clavulanic acid combination.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicon dioxide USP/NF
Xanthan gum USP/NF
Hypromellose 5 cps Ph. Eur. / BP
Colloidal anhydrous silica Ph. Eur. / BP
Succinic acid USP/NF
Aspartame BP
Orange flavour dry 0471034 IH
Raspberry flavour 0473005 IH

6.2 Incompatibilities

None known

6.3 Shelf-life

24 months

6.4 Special precautions for storage

The dry powder should be stored in unopened containers in a dry place at below 30°C.Reconstituted suspensions should be stored in a refrigerator (2-8°C) but do not freeze and should be used within seven days . Keep all medicines out of reach of children.

6.5 Nature and contents of container

A carton containing 125 ml clear transparent glass bottle containing 100 ml suspension in powder form each along with Pack Insert.

6.6 Special precautions for disposal < and other handling >

No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Corporate Office:
Unichem Laboratories Limited,
Unichem Bhavan, Prabhat Estate,
S. V. Road, Jogeshwari (West),
Mumbai – 400 102 , INDIA
Phone: 91-22-66888333
Fax: 91-22-26785198/4391

Manufacturing Site:
Unichem Laboratories Limited,
Unit-I, Village Bhatauli Kalan,
Baddi, Dist. Solan (H.P) – 173 205
Himachal Pradesh - 173205
INDIA
Phone: 00-91-1795-245322/244507
Fax: 00-91-1795-244508

8. Marketing Authorization Number : B4-6039

9. Date of first authorization/renewal of the authorization : 13th December 2015

10. Date of revision of the text : June 2016